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Inflammatory Potential of Diet and Health: What is the evidence?

Potencial Inflamatório da Alimentação e Saúde: Qual a evidência?

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Abstract

Diet and chronic inflammation have been suggested to be risk factors in the development of some conditions, such as obesity, diabetes *mellitus* type 2, cardiovascular diseases, allergic diseases, some neurodegenerative diseases, and some types of cancer. Actually, the increase of this type of diseases in the last decades, mainly in westernized societies, has been associated with dietary patterns and lifestyle changes.

The Mediterranean dietary pattern is recognized as a health promoter model by antioxidant, anti-inflammatory and immunomodulatory properties, and has been studied as a preventive factor for inflammatory diseases. Some components of Mediterranean Diet, such as an increased intake of dietary fibre result by an increased consumption of fruit and vegetables, legumes, whole grains, and nuts, a higher proportion of unsaturated fat from the olive oil, nuts and fatty fish, underlines the protective effect of this dietary pattern against the incidence of chronic diseases.

Recently two new tools have been developed to evaluate the diet's inflammatory potential, the Dietary Inflammatory Index and the Empirical Dietary Inflammatory Pattern score. Many studies showed that diets with a higher inflammatory potential were associated with a higher prevalence of a variety of outcomes, such as obesity, diabetes *mellitus* type 2, cardiovascular diseases, asthma and other allergic diseases, some neurodegenerative diseases and some types of cancer.

This monography reflects a literature review, which the purposes is to examine the association between the inflammatory potential of diet, measured by the Dietary Inflammatory Index and the Empirical Dietary Inflammatory Pattern score, and the health outcomes.

Keywords:

Inflammatory Potential of Diet; Dietary Inflammatory Index; Empirical Dietary Inflammatory Pattern Score; Mediterranean Diet; Inflammation.

Resumo

A alimentação e a inflamação crónica são fatores de risco modificáveis no desenvolvimento de condições como a obesidade, diabetes *mellitus* tipo 2, doenças cardiovasculares, doenças alérgicas, algumas doenças neurodegenerativas e alguns tipos de cancro. O aumento da prevalência deste tipo de doenças nas últimas décadas, principalmente nos países ocidentais, tem sido associado a alterações nos padrões alimentares e estilos de vida.

O padrão alimentar Mediterrânico é reconhecido como um padrão alimentar promotor de saúde devido às suas propriedades antioxidantes, anti-inflamatórias e imunomoduladoras, desempenhando um papel preventivo em várias doenças inflamatórias. Alguns dos componentes presentes neste padrão alimentar como a ingestão aumentada de fibra alimentar, devido a um consumo aumentado de hortofrutícolas, leguminosas, cereais inteiros e frutos gordos, e de uma maior proporção de gordura insaturada proveniente do azeite, frutos gordos e do peixe gordo, parece estar na base do efeito protetor deste padrão alimentar contra a incidência de doenças crónicas.

Recentemente, foram desenvolvidas duas novas ferramentas, o *Dietary Inflammatory Index* e o *Empirical Dietary Inflammatory Pattern score*, que permitem avaliar o potencial inflamatório da alimentação. Diversos estudos têm mostrado que padrões alimentares com um maior potencial inflamatório se encontram associados a uma maior prevalência de obesidade, diabetes *mellitus* tipo 2, doenças cardiovasculares, asma e doenças alérgicas, algumas doenças neurodegenerativas e alguns tipos de cancro.

A presente monografia traduz uma revisão da literatura, que tem por objetivo mostrar o efeito do potencial inflamatório da alimentação, medido pelo *Dietary*

Inflammatory Index e pelo *Empirical Dietary Inflammatory Pattern score*, na saúde da população.

Palavras-chave:

Potencial Inflamatório da Alimentação; *Dietary Inflammatory Index*; *Empirical Dietary Inflammatory Pattern Score*; Alimentação Mediterrânica; Inflamação.

Abbreviations

AA: Arachidonic acid

CVD: Cardiovascular diseases

DASH Score: Dietary Approaches to Stop Hypertension Score

DHA: Docosahexaenoic acid

DII: Dietary inflammatory index

EDIP: Empirical dietary inflammatory pattern

EPA: Eicosapentaenoic acid

FEV1: Forced expiratory volume during the first second

HbA1c: Glycosylated hemoglobin A1c

HDL-C: High-density lipoprotein cholesterol

HEI: Healthy Eating Index

HR: Hazard ratio

hs-CRP: high sensitivity C-reactive protein

ICAM-1: Intercellular adhesion molecule 1

LC-PUFA: Long-chain polyunsaturated fatty acids

LDL-C: Low-density lipoprotein cholesterol

MD: Mediterranean diet

MedDiet Score: Mediterranean Dietary Pattern Score

MUFA: Monounsaturated fatty acids

OR: Odds ratio

PUFA: Polyunsaturated fatty acids

ROS: Reactive oxygen species

RR: Relative risk

SCFA: Short-chain fatty acids

SFA: Saturated fatty acids

TFA: *trans* fatty acids

TLRs: Toll-like receptors

T2DM: Type 2 diabetes *mellitus*

VCAM-1: Vascular cell adhesion protein 1

Contents

Introduction

Inflammation is a natural, healthy reaction of the immune system to tissue injury and it is characterized by increased circulating levels of inflammatory markers[1-6]. One of the fundamental characteristics of all chronic diseases is the initiation of a low-grade inflammation for the entire life, which is frequently caused by lifestyle[1-4, 6-10]. Even though there are multiple factors that contribute to this process, including smoking habits, physical inactivity, excessive alcohol consumption, gender and age, dietary patterns have a significant impact and may modulate it[3, 4, 7, 10].

For years there has been an emphasis on the association between isolated nutrients and disease, leading to simplistic inferences[11]. This is so because the intake of isolated or even multiple food compounds may not produce similar effects as would occur from consuming the whole food[12]. Thus, dietary patterns have been studied, because they represent the overall combination of foods commonly consumed and the synergistic effects between them, which allows a better association between food and health[12]. One of the most well studied dietary patterns is the Mediterranean Diet (MD) which, because it is a model of healthy eating, have been consistently associated with lower risk of clinical events[5, 7, 8, 12-14]. On the other hand, unhealthy dietary patterns, such as Western-style Diets, which are high in refined grains, red meat, and vegetable oils, have been associated with higher risk of inflammation-related diseases[4, 5, 9].

Thus, understanding the inflammatory potential of diet may be useful for the prevention of some chronic diseases[4]. So, diet quality indexes that reflect the inflammatory potential of diet were developed: the Dietary Inflammatory Index (DII) and the Empirical Dietary Inflammatory Pattern (EDIP) score[6, 8, 15].

The purpose of this work is to provide a review of the current published literature on the association between the inflammatory potential of diet and health outcomes.

1. Overview of Inflammation

The inflammatory reaction is a physiological response from the human body, acting as an attempt to protect against antigenic external aggressions[1, 16-18]. With the purpose of controlling the inflammation and reestablishing homeostasis, the immunological system triggers a set of common cellular pathways[1, 19]. The strange organisms are recognized by the host's cells, specially macrophages, using their Toll-like receptors (TLRs). The interaction between the TLRs and their ligands triggers a series of intracellular pathways, from which the NF-kB system activation is particularly important[18, 19]. The macrophage activation allied with an increased phagocytic activity and an increased release of inflammatory mediators will lead to the tracking and neutralizing of the aggressor agent[18, 20]. This abundant cellular proliferation and migration induced by the factors generated in the inflammatory center will cause redness, pain, swelling, heat and loss of function[17, 19].

As the aggressor agent is being eliminated and the inflammation is getting controlled, anti-inflammatory mechanisms are activated[1, 19, 20]. This process involves the secretion of anti-inflammatory mediators and the inhibition of the pro-inflammatory pathways[1, 19]. However, the inability to solve the inflammation can turn a normal inflammatory response into a chronic one[17, 19].

1.1. Types of Inflammation

The inflammatory response can be either acute or chronic, and it's the interactions between multiple cells that determine those settings[1].

The role of low-grade inflammation in many chronic diseases has been demonstrated in several recent studies, such as in cancer, cardiovascular diseases (CVD), type 2 diabetes mellitus (T2DM), allergic diseases, and neurodegenerative diseases[2, 21-23]. In spite of being a prolongation of a previous acute inflammatory state, this kind of inflammation usually starts silently in a less intensive way. Therefore, chronic

inflammation is a state of prolonged inflammation characterised by single nucleus cell agglomerates, cell destruction induced by the presence of the aggressor agent and the attempting of cicatrization, all of them simultaneously[1, 19, 24]. There is a recruiting of the circulating monocytes, which will recruit macrophages to the inflammatory center, local proliferation and immobilization of the macrophages in that spot, tissue destruction caused by the active macrophages' products and the inflammatory cascade, and substitution of the injured tissue for conjunctive tissue[24].

1.2. Inflammatory Markers

In order to understand the role of diet in the inflammatory response is necessary to identify some inflammatory markers. However, there is no consensus on what are the markers that best identify chronic inflammation or which differentiate better acute and chronic inflammation[19, 25]. Thus, a wide variety of cellular markers are described in the literature (number of total leukocytes, monocytes and granulocytes) and soluble mediators (acute phase proteins (CRP, serum A amyloid, fibrinogen), cytokines and chemokines (TNFα, IL-1, IL-6, IL-8), adhesion molecules (VCAM-1, ICAM-1, E-selectin, P-selectin), and adipokines (adiponectin))[19, 24, 25].

Nevertheless, the use of these markers as low-grade inflammation determinants is still a controversial topic. The markers above are nonspecific markers of acute phase response, not representing, by themselves, chronic inflammation[19, 25]. Besides that, there are several factors, such as age, genetics, diet, physical activity, body fat, microbiota, that affect serum concentrations of these markers[25]. On the other hand, the arachidonic acid (AA):eicosapentaenoic acid (EPA) ratio is a more stable and reliable chronic inflammation marker[26]. Still, for each disease, it's exposed in table 1, a not very exhaustive list of commonly reported inflammatory markers in the literature.

2. Diet and Inflammation

Different nutrients, foods and dietary patterns have a different effect on chronic diseases, due to their anti or pro-inflammatory potential. The association between diet and inflammation is described in literature through three approaches to assess dietary intake: isolated nutrients, foods and dietary patterns[27, 28].

2.1. Nutrients and Inflammation

Fatty Acids: In the last few years there has been an increase in the consumption of o n-6 polyunsaturated fatty acids (n-6 PUFA) compared to n-3 (n-3 PUFA), which altered the balance of eicosanoids in favour of AA, which has greater pro-inflammatory effect[26, 29, 30]. However, it is the increase of n-6:n-3 ratio that contributes to the increased incidence of chronic diseases[26, 31].

The current evidence suggests that n-3 PUFA can modulate inflammation, by activating the anti-inflammatory PPAR-γ, which interacts with NF-kB preventing its nuclear translocation[26, 32]. Calder et al. demonstrated that n-3 PUFA can decrease the production of inflammatory mediators, competitively inhibiting the metabolism of AA, increase the production of eicosanoids from EPA, which are weakly inflammatory, and increase production of inflammation resolving resolvins and protectins[31-33]. Furthermore, epidemiologic studies have shown that the increase in the proportion of n-3 PUFA in the diet decrease the expression of adhesion molecules and production of inflammatory cytokines, decrease generation of intracellular signals due to disruption of membrane lipid rafts[32-34]. Studies using animal models have demonstrated that dietary saturated fats raise blood lipids levels only when the diet is deficient in n-3 PUFA[35].

On the other hand, *trans* fatty acids (TFA) have a strong pro-inflammatory potential, being present in small amounts in ruminant animals' products, and in high quantities in baked goods, packaged snacks, and shortenings[12, 36]. Usual dietary patterns have

low "natural" TFA and these do not associate with CVD risk. However high TFA intake from hydrogenated oils is consistently associated with a higher risk of coronary heart disease[36, 37].

Dietary Fibre: Dietary fibre has been target of major investigation given the possibility to exert beneficial effects on the inflammatory state. The dietary fibre has immunomodulatory effects on the gut microbiota balance[38]. Soluble fibre pass through the small intestine and can be fermented by the large intestinal microbiota to produce short-chain fatty acids (SCFA) (acetate, propionate, and butyrate), which activate GPR43 receptors, thereby stimulating production of anti-inflammatory mediators[21, 30, 39-41]. SCFA, in addition to trophic function engaged in enterocytes, also promote epithelial integrity of the intestine and immunological effects, including cytokines and inflammatory chemokines suppression, and a reduction in the production of adhesion molecules[28, 39, 42]. Moreover, the consumption of high-fat diets results in an elevated lipopolysaccharides level in the cell wall of gram-negative bacteria, inducing low-grade inflammation[39].

Studies suggest that increased dietary fibre intake is associated with decreased mortality from CVD and lower incidence of some types of cancer, T2DM, obesity and inflammatory diseases[28, 38, 43].

Polyphenols: Another important group of nutrients that have a protective role in the development of some chronic diseases are the bioactive polyphenols, which include flavonols (in onions, broccoli, tea, and some fruits), flavones (in parsley and celery), flavanones (in citrus fruits), flavanols (flavan-3-ols) such as catechins (in cocoa, apples, grapes, red wine and tea), anthocyanidins (in berries), and isoflavones (in soy)[12, 44, 45]. Current evidence demonstrate that these compounds have benefits on blood pressure, endothelial function, blood lipids and inflammatory markers[12, 44, 45].

They have an anti-inflammatory potential, result of their ability to reduce the formation of reactive oxygen species (ROS) and inhibit the activation of NF-κB[26, 45]. Resveratrol, naturally present in berries, peanuts, and in greater amounts in the skin of red grapes, has a particular interest, due to their antioxidant and anti-inflammatory effect[11]. After all, it's not yet established the doses that cause these benefits, due to the heterogeneity of the various polyphenols and their dietary sources[12].

2.2. Foods and Inflammation

Several epidemiological studies have focused their research on a possible protective effect of some foods, due to the synergistic health effects between their nutrients.

Fruit/Vegetables/Whole grains/Legumes: A high consumption of fruits, vegetables, whole grains and legumes is associated with a reduction of oxidative stress and improvement of lipid profile and insulin sensivity, since they are rich in antioxidant vitamins (β-carotene, vitamin C, E and selenium), polyphenols and fibre, which impart antioxidant and anti-inflammatory properties[40, 46, 47]. The cruciferous vegetables due to their content in phytochemicals, such as glucosinolates, can modulate the activity of carcinogen-metabolizing enzyme systems which have a protective effect on colorectal, breast, prostate and lung cancer[48].

Nuts: Nuts consumption has a cardio-protective effect, possibly due to an improvement in the lipid profile. A high proportion of monounsaturated fatty acids (MUFA) and α-linolenic acid (specially in walnuts), dietary fibre, phytosterols and phenolic antioxidants, minerals (magnesium, zinc, selenium), vitamins (E, B_6, folate), and L-arginine, may modulate inflammatory response and redox status[49, 50]. A recent cross-sectional analysis of the Nurses' Health Study and Health Professionals Follow-Up Study observed that nuts consumption is inversely related to the CRP, IL-6,

TNFR2 and fibrinogen levels, supporting the hypothesis that nuts' antioxidants may reduce inflammation and oxidative stress[49].

Olive oil: Extra virgin olive oil is another food with anti-inflammatory potential, because of its components such as vitamin E, carotenoids and phenolics, and consequent protective effect in cardiovascular risk[51-53], highlighting studies that refer it as a favorable influence in face of the development of neurodegenerative diseases[54]. The established association is based not only on their fatty acids content, but also on the high amounts of phenolic compounds, increased in virgin olive oil, and its consumption repercussions in the reduction of the harm from lipid oxidation, in the decreasing of the inflammatory state and also in the improvement of the endothelial function[54]. The PREDIMED study[55], which aimed to assess the long-term effects of the MD in adults at high risk of CVD, showed that the MD, when supplemented with extra virgin olive oil or mixed nuts was very effective in primary prevention of CVD, reducing the risk of CVD by 30% compared with the control diet group[55, 56].

Fish: A moderate and regular fish intake plays an important role in the promotion of health, in the prevention of chronic diseases and in the improvement in cognitive function, most likely due to its n-3 LC-PUFA content, especially EPA and DHA[57, 58]. Fatty fish, like salmon, sardine and tuna, are a high source of n-3 PUFA with potential anti-inflammatory properties, inhibiting AA metabolism[59]. Other components than n-3 LC-PUFA present in fish, such as taurine and choline, some minerals, especially selenium and zinc, and vitamins B_{12} and D, have been reported to be associated in protection against CVD and diabetes due to the reduction on inflammatory markers[58].

Wine: In fact, in certain circumstances red wine appears to be associated with a reduction, due to the reduction of blood pressure, inhibition of LDL oxidation, improvement of the endothelial function and reduction of the levels of inflammation

and cell adhesion molecules[12, 60, 61]. However, it is unclear what are the components that determine this association, whether it is ethanol itself, the bioactive polyphenols, such as resveratrol or both[61]. Some studies show that the consumption of red wine is associated with lower levels of inflammatory markers, through the inhibition of intracellular signaling pathways and reduced oxidative stress[17].

2.3. Dietary Patterns and Inflammation

Mediterranean Dietary Pattern: The traditional MD is recognized as a health promoter model, by antioxidant and immunomodulatory properties in T2DM, metabolic syndrome, obesity, CVD, cancer, neurodegenerative diseases, asthma and allergic diseases[2, 8, 62, 63]. It is characterized by a high intake of vegetables, fruit, legumes, nuts, leaves, and whole grains; a high intake of MUFAs, mainly in form of olive oil, but a low intake of saturated fatty acids (SFA); a high fish consumption, depending on sea proximity; a reduced intake of red and processed meat; a moderate intake of dairy products, mainly cheese and yogurt; and a regular but moderate ethanol consumption, mainly in the form of wine and generally during meals[62].

An increased intake of dietary fibre and micronutrients with antioxidant properties, resulting from higher fruit and vegetable, legumes, and nuts consumption and a higher proportion of MUFA and PUFA from olive oil, nuts and fatty fish, together with the small daily intake of SFA, underlines the protective effect of this dietary pattern against the incidence of chronic diseases[62, 64, 65]. The reduction in blood pressure, improvements of lipid profile and insulin resistance, and the reduction of inflammatory markers, seem to be the basis of the reported protective effect[65, 66]. Regarding the preventive capacity of MD in neoplasic diseases, studies show an inverse association between MD and prostate, breast, stomach, colorectal cancer and melanoma[8, 63, 67]. Underlining the role of dietary fibre and the diversity of compounds with antioxidant properties[46] such as vitamin C, E, selenium, magnesium, zinc and carotenoids, and

n-3 LC-PUFA mainly present in fish[58]. Regarding the development of T2DM, a protective effect is described in the literature associated with a greater intake of dietary fibre, a decreased intake of refined cereals and greater amount of unsaturated fat[68, 69].

3. How to Measure Inflammatory Potential of Diet?

Indices that assess dietary patterns are more predictive of diet-disease associations than a more specific approach that use foods or nutrients isolated[70]. Therefore, two tools were recently developed and validated that allow us to evaluate the inflammatory potential of diet, but they differ in concept and design (Table 2). There are other dietary indices, such as HEI, followed the Dietary Guidelines for Americans 2005, DASH Score, that are more focused on a specific health benefit, and MedDiet Score, that try to assess the level of adherence to the MD. All of these indices represent a dietary scoring pattern that represents healthfulness of the diet. However, none was specifically developed to assess the inflammatory potential of diet[7].

3.1. Dietary Inflammatory Index

The DII was recently developed and categorizes individuals' diet according to their inflammatory potential from maximal pro to anti-inflammatory based on the evaluation of the effect of nutrients and foods on plasma concentrations of 6 inflammatory markers : IL-1β, IL-4, IL-6, IL -10, TNFα and CRP[5, 15, 70].

This index was proposed and validated by Cavicchia et al. in 2009, in which it was observed an inverse association between the DII and the serum concentration of CRP[5, 70]. Later, in 2014, Shivappa et al. set this tool and validated it in the SEASONS prospective study[15]. The DII modified by Shivappa et al. was developed through a systematic review of the literature about the relationship between 45 dietary parameters and 6 inflammatory markers, in which 1943 articles were identified and

scored[15, 70]. These articles were classified according to the effect of the specific dietary parameter on the inflammatory effect, and was assigned the score of +1 if it indicated a pro-inflammatory effect (significant increase in IL-1β, IL-6, TNFα or CRP, or decrease in IL-4 or IL-10); 0 if there was no change in inflammatory markers; and -1 if indicated an anti-inflammatory effect (significant decrease IL-1β, IL-6, TNFα or CRP, or increase in IL-4 or IL-10)[15, 70].

3.2. Empirical Dietary Inflammatory Pattern Score

More recently, an EDIP score was also developed in order to evaluate the inflammatory potential of diet, exclusively based on the assessment of the effect of food groups[70, 71]. This index was proposed and validated in a cohort study, Nurses' Health Study, through the evaluation of 39 previously chosen food groups and applied in reduced rank regression models, in order to identify a more predictive dietary pattern of 3 plasma inflammatory markers: IL-6, CRP and TNFαR2[3, 71]. Stepwise regression analyses identified 18 food groups that have been weighted and summed up for each participant. Therefore, the EDIP score is the sum of 18 food groups, being that: positive scores indicate a more pro-inflammatory effect; and negative scores indicate a more anti-inflammatory effect[3, 70, 71].

4. Evidence of Inflammatory Potential of Diet and Health

4.1. Inflammatory Potential of Diet and Cardiometabolic Health

It is now evident that dietary factors influence diverse cardiometabolic risk factors, including not only obesity and LDL-C but also inflammation, blood pressure, oxidative stress, glucose-insulin homeostasis, hepatic, cardiac and endothelial function, visceral adiposity and the microbiome[12].

In the SU.VI.MAX study[72] conducted in a cohort of 3726 individuals, it was demonstrated that a more pro-inflammatory diet, measured by the DII, was

associated with an increased risk of myocardial infarction by 2,24 times, and with a worse cardio metabolic profile. A meta-analysis also showed that a greater adherence to the MD reported a significant decrease of IL-6, CRP levels and adhesion molecules, reducing inflammation and improving endothelial function[73]. Regarding the T2DM, subjects in the highest DII quintile had approximately 3.02 greater odds of T2DM[22]. These results reinforce the importance of promoting an anti-inflammatory diet as a strategy in the prevention of cardiometabolic diseases[2, 10, 74].

On the other hand, the adherence to a more anti-inflammatory dietary pattern may also be used as a means of disease control. A study of 454 patients candidates for coronary artery bypass grafting, showed that a more pro-inflammatory diet was associated with a higher diabetes and myocardial infarction prevalence and a worse lipid profile[6]. Therefore, the promotion of a more anti-inflammatory dietary pattern would help in the prevention of recurrent cardiovascular events whether in this group of patients or in those who have a high cardiovascular risk[74].

4.2. Inflammatory Potential of Diet and Neurodegenerative Diseases

It is known that diet and lifestyle affect health and longevity, by changing telomere length, a marker for estimating cellular aging[13]. In that context, several human studies have shown an association between the DII and the rate of telomere shortening. In the PREDIMED-Navarra study[13], higher DII was associated with a nearly two-fold higher risk of accelerated telomere shortening during a follow-up period of five years. In fact, a greater intake of antioxidant vitamins, polyphenols, curcumin and PUFA n-3, were associated with longer telomeres, and consequently a lower risk of age-related diseases[13].

In addition, a dietary pattern with a greater inflammatory potential has been associated with a more marked decline of cognitive function and an increased risk of dementia[75]. In the Women's Health Initiative Memory Study, dietary patterns with

the greatest pro-inflammatory potential have been associated with a 27% risk of cognitive decline or dementia increase[76]. However, the differences between cognitive performance among the groups with the highest and lowest score were not clinically significant. Nevertheless, the cumulative long-term effect may be relevant.

A large number of studies reported the possible role of inflammation in depression through hypothalamic-pituitary-adrenal axis activation, tryptophan depletion and decreased availability of brain-derived neurotrophic factor[77, 78]. The SUN cohort study[78] showed that the participants with the highest DII had an increased risk of 47% of develop depression. One of the most remarkable results obtained in this study showed that a pro-inflammatory diet could be particularly damaging in individuals with other cardio metabolic conditions or among those aged ≥55 years[78].

Moreover, studies have been conducted in subjects with multiple sclerosis and previous research reported a positive association between the consumption of a more pro-inflammatory diet and the risk of multiple sclerosis (OR=1,66)[79].

4.3. Inflammatory Potential of Diet and Cancer

Significant associations were observed between inflammatory potential of diet and colorectal[8, 23, 80, 81], prostate[82] and breast[83] cancer. Thus, a more anti-inflammatory dietary pattern can contribute to the reduction of risk through improving vascular, immune and inflammatory function[9]. Shivappa et al., in a prospective cohort study, showed 110% increased risk of death by digestive tract cancer in individuals at tertile 3 compared to tertile 1[2]. Also, the current evidence shows that the consumption of a more pro-inflammatory diet, reflected by higher scores DII and EDIP score, is associated with an increased risk of colorectal cancer[3, 8, 9, 23, 80, 81]. Although more studies are needed, a more pro-inflammatory diet through the promotion of an pro-inflammatory cell environment, the dysregulation of multiple metabolic risk factors such as insulin resistance, increased oxidative stress through the activation of cyclo-

oxygenase-2 enzyme in colon epithelial cells, changes in the intestinal microbiota composition, and possible epigenetic changes may increase the tumorigenesis and lead to an increased risk of developing colorectal cancer[3, 9, 80]. Thus, the promotion of a more anti-inflammatory diet, with foods rich in fibre and phytochemicals, may be a strategy of prevention as a means of reducing the risk of colorectal cancer.

On the other hand, the perception of the inflammatory potential of diet can also be used as a means of disease control. A retrospective cohort study showed that dietary patterns can have an impact on survival after a diagnosis of prostate cancer with a worse prognosis[82]. The mechanism is still unclear, but one of the hypotheses is that inflammatory state interferes with the therapy, causing treatment resistance[82]. So, this can be a viable and less expensive intervention to reduce mortality[82].

4.4. Inflammatory Potential of Diet and Allergic Diseases

The prevalence of asthma and other allergic diseases has been increasing in westernized countries[84]. The evidence supports that the increased prevalence of these diseases is due in part to changes in dietary patterns, mainly on the content of phenolic and antioxidants compounds, fibre and modification of fatty acids[84]. However, data that evaluate the inflammatory potential of diet and the occurrence of asthma and atopy are still scarce[21, 85].

A study conducted in Australia showed that asthmatic individuals had a DII score higher than the healthy controls[21]. Lisa Wood et al., demonstrated a positive association between IL-6 levels and FEV1 and the DII score, suggesting that systemic inflammation induced by diet may contribute to the impairment of pulmonary function[21]. Previous studies have also shown that a high adherence to the MD, increasing the consumption of fruits and vegetables[84], nuts[31] and fish[84, 86] in detriment of other foods, are associated with better asthma control and pulmonary function improvement.

Therefore, dietary patterns seem to potentially contribute to the inflammatory environment in asthmatic individuals. Thus, the promotion of a diet with a greater anti-inflammatory potential in asthmatic patients may be a useful strategy to improve clinical outcomes in this disease[21, 84].

Critical Analyses and Conclusions

The first step in the prevention and control of some of the most prevalent chronic diseases goes through limiting pro-inflammatory dietary patterns, combined with an adoption of a more anti-inflammatory diet, like the MD[5, 7, 8, 12-14]. This review shows consistent and significant associations between the higher inflammatory potential of diet and the incidence of some chronic diseases in the general population independently of study design. Therefore, the increased adherence to an anti-inflammatory diet characterised by a high intake of fruits and green leafy vegetables, nuts, olive oil and fatty fish, and decreased intake of pro-inflammatory components, such as processed meat, vegetable oils and refined grains, may play an important role in reducing the risk of these chronic diseases[62, 64, 65].

Dietary patterns capture multiple dietary factors and may be more predictive of disease processes and outcomes, because it considers synergistic or antagonistic interactions between nutrients and foods[70, 71]. There are several approaches to evaluate the food quality. The HEI, DASH and MedDiet scores are some of the most used indexes, and all of them have been associated with reducing the risk of mortality from all causes[7]. In contrast, the DII and EDIP scores represent a recently new index to evaluate dietary patterns' quality and focus specifically on the diet's inflammatory potential. Therefore, the whole diet is taken into account, including micronutrients, macronutrients and bioactive compounds commonly consumed and some foods, not just nutrients or foods isolated[3, 15, 70, 71].

Despite that, these tools are not devoid of limitations. A limitation of DII and EDIP scores is that these nutrients or foods are consumed with other food items[2]. In addition, a dietary pattern may be associated with other modifying factors not included in the studies. Thus, these factors together may attenuate or accentuate the association[23]. Furthermore, different studies use different food parameters which difficult the comparison and may lead to unaccurate interpretations.

Regarding the EDIP score, the major limitation is the fact that it was validated in a cohort study, Nurses' Health Study, whose sample were only female individuals. Moreover, despite this index assess the inflammatory potential of diet the choice of food groups is controversial. Among the 18 components, other fish than dark-meat fish and tomatoes were positively associated with inflammatory markers, whereas pizza was inversely related[71]. The explanation for this association may be the culinary methods used (frying, grilling or roasting) that increase the concentration of advanced glycation end products which are known to have pro-inflammatory features[87], and possibly the higher bioavailable lycopene in tomato sauce than fresh tomatoes[71, 88]. Still, in my opinion, the selection of the food groups wasn't the best, as it was not able to properly assess the inflammatory potential of a dietary pattern.

In conclusion, inflammation is an important mechanism linking dietary patterns and some chronic diseases development. The promotion of a more anti-inflammatory dietary pattern, such as the MD, should be used as a prevention strategy but also as a form of control reported along the review. The most studies have been conducted with adults and older adults, so it is essential to develop further research not only with these groups of population as between the youngers, due to limited evidence that exists in this area.

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Attachments

Table 1. Inflammatory markers in specific diseases.

	CVD [6, 19, 89]	***Obesity*** [19]	***Type 2 DM*** [19]	***Allergic Diseases*** [19, 21]	***Neurodegenerative Diseases*** [19]	***Cancer*** [3, 90, 91]
Acute phase proteins	CRP Fibrinogen SAA	CRP Fibrinogen SAA	CRP Fibrinogen SAA		CRP	CRP
Cytokines	MCP-1, TNFα, TNFβ, IL-1, IL-3 IL-6, IL-8, IL-18	TNFα, IL-1 IL-6, IL-8 IL-17, IL-18	TNFα, IL-1 IL-6, IL-8 IL-17, IL-18	TNFα, IL-4, IL-5, IL-6, IL-8, IL-12, IL-13	TNFα IL-6	TNFα, IL-1 IL-6,IL-10 IL-18, IL-4 IL-13, IL-3 TGF-β
Adhesion molecules	VCAM-1 ICAM-1 P-selectin E-selectin	VCAM-1 ICAM-1 E-selectin P-selectin	VCAM-1 ICAM-1 E-selectin P-selectin			
Others		Adiponectin	Adiponectin	IgE		

Table 2. Differences between DII and EDIP[15, 70, 71]

Dietary Index			
		DII	***EDIP***
Predictors		Nutrients and foods	Foods and food groups exclusively
Inflammatory markers		6 inflammatory markers (CRP, TNFα, IL-6, IL-1β, IL-4, IL-10)	3 inflammatory markers (CRP, TNFαR2, IL-6)
Food parameters		45 food parameters (36 anti-inflammatory, 9 pro-inflammatory)	18 food parameters (9 anti-inflammatory, 9 pro-inflammatory)
Food parameters	**Pro-inflammatory**	Energy	Processed meat
		Carbohydrates	Organ meat
		Protein	Red meat
		Total fat	Other fish (other than dark-meat fish)
		SFA	Tomatoes
		trans fat	Other vegetables (other than green leafy vegetables and dark yellow vegetables)
		Cholesterol	Refined grains
		Vitamin B_{12} (Cobalamin)	High-energy beverages (cola and other carbonated beverages with sugar)
		Iron	Low-energy beverages (low-energy cola and other low-energy carbonated beverages)
	Anti-inflammatory	PUFA	Dark yellow vegetables (comprising carrots, yellow squash, and sweet potatoes)
		n-3 PUFA	
		n-6 PUFA	
		MUFA	
		Dietary fibre	Green leafy vegetables
		Vitamin A	
		β-carotene	
		Vitamin D	
		Vitamin E	Fruit juices
		Vitamin B_1 (Thiamine)	
		Vitamin B_2 (Riboflavin)	
		Vitamin B_3 (Niacin)	
		Vitamin B_6 (Pyridoxine)	Snacks
		Folic acid	
		Vitamin C (Ascorbic acid)	
		Magnesium	
		Zinc	Pizza
		Selenium	
		Isoflavones	
		Flavan-3-ol	
		Flavones	Wine
		Flavonols	

Table 2. Differences between DII and EDIP (Continued)

	Flavonones	
	Anthocyanidins	
	Alcohol	Beer
	Caffein	
	Green or black tea	
	Garlic	
	Onion	Tea
	Rosemary	
	Oregano	
	Ginger	
	Saffron	Coffee
	Turmeric	
	Pepper	
Statistical Methods	Standardization, normalization	Reduced rank regression, stepwise linear regression
Final Score	45 components, weighted and summed to derive the score for each individual	18 components, weighted and summed to derive the score for each individual
Score Interpretation	Higher scores indicate pro-inflammatory diets. Lower scores indicate anti-inflammatory diets.	

Note.

Processed meat - hot dogs, processed meats, bacon; **Red meat**; **Organ meat** – livers; **Other fish** - canned tuna, shrimp, lobster, scallops, other seafood than dark meat fish; **Tomato** - fresh tomato; **Other vegetables** - corn, mixed vegetables, eggplant, celery, alfalfa sprouts, mushrooms, green/yellow/red peppers, zucchini, cucumbers; **Refined grain** - white bread, white rice, bagels, muffins, biscuits, pasta, pancakes, waffles, refined breakfast cereals; **High-energy beverage** – Cola and other carbonated beverages with sugar; **Low-energy beverage** - Low-energy cola and other low-energy carbonated beverages

Green leafy vegetable - spinach, iceberg or head lettuce, romaine or leaf lettuce; **Dark yellow vegetable** - carrots, sweet potatoes, winter squash, yams; **Fruit juice** - apple juice, orange juice, grape juice, prune juice, other juice; **Snack** - potato/corn chips, popcorn, crackers; **Pizza; Wine** - white wine, red wine; **Beer** - beer, light beer; **Tea** - Tea (not herbal); **Coffee** - coffee, decaffeinated coffee;

Table 3. Studies on inflammatory potential of diet and health.

Author (reference)	*Study design, participants*	*Dietary inflammatory potential index*	*Nutrients and food parameters used in dietary inflammatory potential index*	*Inflammatory markers used in dietary inflammatory potential index*	*Outcomes*	*Associations/Effects observed*
Inflammatory potential of diet and cardio metabolic health						
Neufcourt et al. *(72)*	13 years randomized, double-blind, placebo-controlled primary prevention trial (SU.VI.MAX), 7743 adults, Female, 35-60 years Male, 45-60 years Daily supplementation with antioxidant vitamins and minerals (Vitamin β-carotene, E C, selenium, and zinc)	Dietary inflammatory index	36 nutrients and food parameters: **Pro-inflammatory:** Energy, carbohydrate, protein, total fat, SFA, cholesterol, vitamin B_{12}, iron **Anti-inflammatory:** PUFA, n-3 PUFA, n-6 PUFA, MUFA, fibre, vitamin A, β-carotene, vitamin D, E, B_1, B_2, B_3, B_6, folic acid, C, magnesium, zinc, isoflavones, flavan-3-ol, flavones, flavonols, flavononones, anthocyanidins, alcohol, tea, garlic, onion, ginger, pepper	6 inflammatory markers: CRP, IL-1β, IL-4, IL-6, IL-10, TNFα	Myocardial infarction Stroke Angina pectoris and revascularization interventions	• Risk of myocardial infarction increased by 2.24 ($HR_{highest\ vs\ lowest}$ = 2.24 (1.08–4.67); 95% CI) for subjects in the 4th quartile • No significant association was observed between the DII and stroke ($HR_{highest\ vs\ lowest}$ = 1.22 (0.56–2.65); 95% CI) or angina pectoris and revascularization interventions ($HR_{highest\ vs\ lowest}$ = 0.73 (0.41–1.30); 95% CI)
Graffouillère et al. (91)	13 years randomized, double-blind, placebo-controlled primary prevention trial (SU.VI.MAX), 8089 adults, Female, 35-60 years Male, 45-60 years Daily supplementation with antioxidant vitamins and minerals (Vitamin C, E, β-carotene, selenium, and zinc)	Dietary inflammatory index	36 nutrients and food parameters: **Pro-inflammatory:** Energy, carbohydrate, protein, total fat, SFA, cholesterol, vitamin B_{12}, iron **Anti-inflammatory:** PUFA, n-3 PUFA, n-6 PUFA, MUFA, fibre, vitamin A, β-carotene, vitamin D, E, B_1, B_2, B_3, B_6, folic acid, C, magnesium, zinc, , isoflavones, flavan-3-ol, flavones, flavonols, flavononones, anthocyanins, alcohol, tea, garlic, onion, ginger, pepper	6 inflammatory markers: CRP, IL-1β, IL-4, IL-6, IL-10, TNFα	Overall mortality Mortality by CVD or cancer Cancer specific mortality	Placebo group: • Risk of overall mortality increased by 2.10 $HR_{highest\ vs\ lowest}$ = 2.10 (1.15–3.84); 95% CI) for subjects in the 3th tertile Antioxidant supplementation group: • No significant association was observed between the DII and overall mortality ($HR_{highest\ vs\ lowest}$ = 1.09 (0.67–1.77); 95% CI) Sex-specific: • Risk of mortality by CVD or cancer increased by 1.53 ($HR_{highest\ vs\ lowest}$ = 1.53 (1.01–2.32); 95% CI) for subjects in the 3th tertile • Risk of mortality by specific cancer mortality increased by 1.83 ($HR_{highest\ vs\ lowest}$ = 1.83 (1.12–2.99); 95% CI) for subjects in the 3th tertile

Table 3. Studies on inflammatory potential of diet and health (Continued).

Author (reference)	*Study design, participants*	*Dietary inflammatory potential index*	*Nutrients and food parameters used in dietary inflammatory potential index*	*Inflammatory markers used in dietary inflammatory potential index*	*Outcomes*	*Associations/Effects observed*
Shivappa et al. [2]	Prospective cohort (NHANES III), 12 366 adults, Female and male, >19 years, Followed for 6 years	Dietary inflammatory index	27 nutrients and food parameters: **Pro-inflammatory:** Energy, carbohydrate, protein, total fat, SFA, cholesterol, vitamin B_{12}, iron **Anti-inflammatory:** PUFA, n-3 PUFA, n-6 PUFA, MUFA, fibre, vitamin A, β-carotene, vitamin D, E, B_1, B_2, B_3, vitamin B6, folic acid, C, magnesium, zinc, selenium, alcohol	6 inflammatory markers: CRP, IL-1β, IL-4, IL-6, IL-10, TNFα	Overall mortality CVD mortality (coronary heart disease or congestive cardiac failure) Cancer mortality Digestive-tract cancer mortality	• Risk of overall mortality increased by 1.34 ($HR_{highest\ vs\ lowest}$ = 1.34 (1.19–1.51); 95% CI) for subjects in the 3th tertile • Risk of CVD mortality increased by 1.46 ($HR_{highest\ vs\ lowest}$ = 1.46 (1.18–1.81); 95% CI) for subjects in the 3th tertile • Risk of cancer mortality increased by 1.46 $HR_{highest\ vs\ lowest}$ = 1.46 (1.10–1.96); 95% CI) for subjects in the 3th tertile • Risk of digestive-tract cancer mortality increased by 2.10 ($HR_{highest\ vs\ lowest}$ = 2.10 (1.15–3.84); 95% CI) for subjects in the 3th tertile
Camargo-Ramos et al. [14]	Cohort, 90 overweight and sedentary adults Female and male ≥18 years, Followed for 1 year	Dietary inflammatory index	26 nutrients and food parameters: **Pro-inflammatory:** Carbohydrate, protein, total fat, SFA, *trans* fat, vitamin B_{12}, iron **Anti-inflammatory:** PUFA, n-3 PUFA, n-6 PUFA, MUFA, fibre, vitamin A, β-carotene, vitamin D, E, B_1, B_2, B_3, vitamin B6, folic acid, C, magnesium, zinc, selenium, caffeine	6 inflammatory markers: CRP, IL-1β, IL-4, IL-6, IL-10, TNFα	Total cholesterol Triglycerides HDL-c LDL-c Glucose Cardio metabolic risk score HbA1c Flow-mediated vasodilation Pulse wave velocity	• A more anti-inflammatory diet was inversely correlated with triglyceride levels (r = -0.354, p<0.05), glucose (r = -0.422, p<0.05), cardio metabolic risk score (r = -0.228, p<0.05), and pulse wave velocity (r = -0.437, p<0.05). • A more anti-inflammatory diet was positively correlated with flow-mediated vasodilation (r = 0.261, p<0.05).

Table 3. Studies on inflammatory potential of diet and health (Continued).

Author (reference)	*Study design, participants*	*Dietary inflammatory potential index*	*Nutrients and food parameters used in dietary inflammatory potential index*	*Inflammatory markers used in dietary inflammatory potential index*	*Outcomes*	*Associations/Effects observed*
Frahangi et al. [6]	Cross-sectional, 454 adults candidates of coronary artery bypass grafting Female and male, 35-80 years	Dietary inflammatory index	30 nutrients and food parameters: **Pro-inflammatory:** Energy, carbohydrate, protein, total fat, SFA, cholesterol, *trans* fat, vitamin B_{12}, iron **Anti-inflammatory:** PUFA, n-3 PUFA, n-6 PUFA, MUFA, fibre, vitamin A, β-carotene, vitamin D, E, B_1, B_2, B_3, vitamin B6, folic acid, C, magnesium, zinc, selenium, caffeine, tea, garlic	6 inflammatory markers: CRP, IL-1β, IL-4, IL-6, IL-10, TNFα	HbA1c Total cholesterol Triglyceride LDL-c HDL-c Hematocrit Creatinine Blood urea nitrogen Lipoprotein (a) CRP	Male: • Triglyceride, total cholesterol, creatinine and blood urea nitrogen were higher in highest quartiles of DII (β= 0.99 (0.98-0.99); 95% CI) • • HDL-c concentration was lower in the highest quartiles of DII (β = -0.95 (0.90-0.99); 95% CI) Female • Lipoprotein (a) was higher in highest quartiles of DII (β = 0.98 (0.96-1.00); 95% CI)
Denova-Gutiérrez et al. [22]	Cross-sectional, 201 adults with T2DM 973 adults without T2DM Female and male, 20–69 years	Dietary inflammatory index	27 nutrients and food parameters: **Pro-inflammatory:** Carbohydrate, protein, total fat, SFA, *trans* fat, cholesterol, vitamin B_{12}, iron **Anti-inflammatory:** PUFA, n-6 PUFA, n-3 PUFA, MUFA, fibre, vitamin A, β-carotene, vitamin E, B_1, B_2, B_3, B6, folic acid, C, alcohol, magnesium, zinc, garlic, onions	6 inflammatory markers: CRP, IL-1β, IL-4, IL-6, IL-10, TNFα	T2DM	• Subjects in the highest DII quintile had approximately 3.02 greater odds of T2DM compared with subjects in the lowest DII quintile ($OR_{highest\ vs\ lowest}$ = 3.02 (1.39–6.58); 95% CI)
Inflammatory potential of diet and neurodegenerative diseases						
Sanchez-Villegas et al. *[78]*	Prospective dynamic cohort (SUN study), 15 093 adults Female, 45-50 years	Dietary inflammatory index	28 nutrients and food parameters: **Pro-inflammatory:** Energy, carbohydrate, protein, total fat, SFA, *trans* fat, cholesterol, vitamin B_{12}, iron **Anti-inflammatory:** PUFA, n-3 PUFA, n-6 PUFA, MUFA, fibre, vitamin A, vitamin D, E, B_1, B_2, B_3, B_6, folic acid, C magnesium, zinc, selenium, alcohol, caffeine	6 inflammatory markers: CRP, IL-1β, IL-4, IL-6, IL-10, TNFα	Incidence of depression	• Risk of developing depression was 47% higher in the most pro-inflammatory group ($HR_{highest\ vs\ lowest}$ = 1.47 (1.17-1.85); 95% CI)

Table 3. Studies on inflammatory potential of diet and health (Continued).

Author (reference)	*Study design, participants*	*Dietary inflammatory potential index*	*Nutrients and food parameters used in dietary inflammatory potential index*	*Inflammatory markers used in dietary inflammatory potential index*	*Outcomes*	*Associations/Effects observed*
Shivappa et al.[77]	Prospective cohort (Australian Longitudinal Study on Women's Health), 13 715 adults Female, 45-50 years Followed for 5 years	Dietary inflammatory index	26 nutrients and food parameters: **Pro-inflammatory:** Energy, carbohydrate, protein, total fat, SFA, cholesterol, iron **Anti-inflammatory:** PUFA, n-3 PUFA, n-6 PUFA, MUFA, fibre, vitamin A, β-carotene, vitamin E, B_1, B_2, B_3, folic acid, C, magnesium, zinc, alcohol, garlic, onions	6 inflammatory markers: CRP, IL-1β, IL-4, IL-6, IL-10, TNFα	Incidence of depression	• Risk of developing depression was 26% lower in the most anti-inflammatory group ($RR_{lowest\ vs\ highest}$ = 0·81 (0·69-0·96); 95% CI)
García-Calzón et al. [13]	Prospective cohort (PREDIMED-NAVARRA), 520 adults with high cardiovascular disease risk Female, 60–80 years, Male, 55–80 years Followed for 5 years	Dietary inflammatory index	32 nutrients and food parameters: **Pro-inflammatory:** Energy, carbohydrate, protein, total fat, SFA, *trans* fat, cholesterol, vitamin B_{12}, iron **Anti-inflammatory:** PUFA, n-3 PUFA, n-6 PUFA, MUFA, fibre, vitamin A, β-carotene, vitamin D, E, B_1, B_2, B_3, B6, folic acid, C, magnesium, zinc, selenium alcohol, caffeine, tea, garlic, onion	6 inflammatory markers: CRP, IL-1β, IL-4, IL-6, IL-10, TNFα	Telomere shortening	• Subjects in the highest DII quintile had approximately 1.80 greater odds of shorter telomeres compared with subjects in the lowest DII quintile ($OR_{highest\ vs\ lowest}$ = 1.80 (1.03–3.17); 95% CI)
Shivappa et al.[79]	Case-control 60 adults with multiple sclerosis 140 controls hospitalized for acute non-neoplastic diseases Female and male, 20-60 years	Dietary inflammatory index	27 nutrients and food parameters: **Pro-inflammatory:** Carbohydrate, protein, total fat, SFA, cholesterol, vitamin B_{12}, iron **Anti-inflammatory:** PUFA, n-3 PUFA, n-6 PUFA, MUFA, fibre, vitamin A, β-carotene, vitamin E, B_1, B_2, B_3, B6, folic acid, C, magnesium, zinc, selenium, onion, pepper	6 inflammatory markers: CRP, IL-1β, IL-4, IL-6, IL-10, TNFα	Multiple sclerosis	• Subjects with the highest DII score had approximately 1.66 greater odds of multiple sclerosis compared with subjects with the DII score ($OR_{highest\ vs\ lowest}$ = 1.66 (1.19–2.31); 95% CI)

Table 3. Studies on inflammatory potential of diet and health (Continued).

Author (reference)	*Study design, participants*	*Dietary inflammatory potential index*	*Nutrients and food parameters used in dietary inflammatory potential index*	*Inflammatory markers used in dietary inflammatory potential index*	*Outcomes*	*Associations/Effects observed*
Hayden et al. [76]	Cross sectional, 1723 adults, Female and male, 60-85 years	Dietary inflammatory index	45 nutrients and food parameters: **Pro-inflammatory:** Energy, carbohydrate, protein, total fat, SFA, *trans* fat, cholesterol, vitamin B_{12}, iron **Anti-inflammatory:** PUFA, n-3 PUFA, n-6 PUFA, MUFA, fibre, vitamin A, β-carotene, vitamin D, A, β-carotene, vitamin D, E, B_1, B_2, B_3, B6, folic acid, C, magnesium, zinc, selenium, isoflavones, flavan-3-ol, flavones, flavonols, flavonones, anthocyanidins, alcohol, caffeine, tea, garlic, onion, rosemary, oregano, ginger, saffron, turmeric, pepper, eugenol	6 inflammatory markers: CRP, IL-1β, IL-4, IL-6, IL-10, TNFα	Incidence of cognitive decline and earlier onset of cognitive impairment	• Risk of incidence of cognitive decline and earlier onset of cognitive impairment increased by 1.27 ($HR_{highest\ vs\ lowest}$ = 1.27 (1.06–1.52); 95% CI) for subjects in the 4th quartile
Inflammatory potential of diet and cancer						
Tabung et al. [81]	Clinical trial (Women's Health Initiative study), 152 536 postmenopausal women without colorectal cancer 50-79 years Followed for 11 years	Dietary inflammatory index	32 nutrients and food parameters: **Pro-inflammatory:** Energy, carbohydrate, protein, total fat, SFA, *trans* fat, cholesterol, vitamin B_{12}, iron **Anti-inflammatory:** PUFA, n-3 PUFA, n-6 PUFA, MUFA, fibre, vitamin A, β-carotene, vitamin D, E, B_1, B_2, B_3, B_6, folic acid, C, magnesium, zinc, selenium, , isoflavones, alcohol, caffeine, tea, onion	6 inflammatory markers: CRP, IL-1β, IL-4, IL-6, IL-10, TNFα	Incidence of colorectal cancer Incidence of proximal colon cancer Incidence of distal colon cancer Incidence of rectal cancer	• Risk of colorectal cancer increased by 1.22 ($HR_{highest\ vs\ lowest}$ = 1.22 (1.05-1.43); 95% CI) for subjects in the 5th quintile • Risk of proximal colon cancer increased by 1.35 ($HR_{highest\ vs\ lowest}$ = 1.35 (1.05-1.67); 95% CI) for subjects in the 5th quintile • No significant association was observed between the DII and distal colon cancer (HR $_{highest\ vs\ lowest}$ = 0.84 (0.61-1.18); 95% CI) and rectal cancer ($HR_{highest\ vs\ lowest}$ = 1.20 (0.84-1.72); 95% CI)

Table 3. Studies on inflammatory potential of diet and health (Continued).

Author (reference)	*Study design, participants*	*Dietary inflammatory potential index*	*Nutrients and food parameters used in dietary inflammatory potential index*	*Inflammatory markers used in dietary inflammatory potential index*	*Outcomes*	*Associations/Effects observed*
Tabung et al. [83]	Clinical trial (Women's Health Initiative study) 161 808 postmenopausal women 50-79 years	Dietary inflammatory index	32 nutrients and food parameters: **Pro-inflammatory:** Energy, carbohydrate, protein, total fat, SFA, *trans* fat, cholesterol, vitamin B_{12}, iron **Anti-inflammatory:** PUFA, n-3 PUFA, n-6 PUFA, MUFA, fibre, vitamin A, β-carotene, vitamin D, E, B_1, B_2, B_3, B_6, folic acid, C, magnesium, zinc, selenium, , isoflavones, alcohol, caffeine, tea, onion	6 inflammatory markers: CRP, IL-1β, IL-4, IL-6, IL-10, TNFα	Incidence of invasive breast cancer Invasive breast cancer mortality	• No significant association was observed between the DII and incidence of breast cancer (HR $_{\text{highest vs lowest}}$ = 0.99 (0.91-1.07); 95% CI) • Risk of invasive breast cancer mortality increased by 1.33 (HR $_{\text{highest vs lowest}}$ = 1.33 (1.01-1.76); 95% CI) for subjects in the 5th quintile
Liu L et al. [3]	Prospective cohort, 124 433 adults and health professionals Female, 30-55 years Male, 40-75 years Followed for 10 years	Empirical dietary inflammatory pattern	18 foods and food groups: **Pro-inflammatory:** Processed meat, organ meat, red meat, other fish, tomatoes, other vegetables, refined grains, high-energy beverages, low-energy beverages **Anti-inflammatory:** Beer, wine, tea, coffee, dark yellow vegetables, leafy green vegetables, fruit juice, snacks, pizza	3 inflammatory markers: IL6, CRP, TNFαR2	Colorectal cancer with an absent or low peritumoral lymphocytic reaction Colorectal cancer with an high peritumoral lymphocytic reaction	• Risk of colorectal cancer with an absent or low peritumoral lymphocytic reaction increased by 2.60 (HR $_{\text{highest vs lowest}}$ = 2.60 (1.60-4.23); 95% CI) for subjects in the 5th quintile • No significant association was observed between the EDIP and colorectal cancer with an high peritumoral lymphocytic reaction (HR $_{\text{highest vs lowest}}$ = 0.91 (0.57-1.45); 95% CI, Ptrend = 0.99)

Table 3. Studies on inflammatory potential of diet and health (Continued).

Author (reference)	*Study design, participants*	*Dietary inflammatory potential index*	*Nutrients and food parameters used in dietary inflammatory potential index*	*Inflammatory markers used in dietary inflammatory potential index*	*Outcomes*	*Associations/Effects observed*
Tabung et al. [23]	Prospective cohort (Health Professionals Follow-up Study: 1986-2012 and Nurses' Health Study: 1984-2012) 74 246 women adults 46 804 men adults Followed for 26 years	Empirical dietary inflammatory pattern	18 foods and food groups: **Pro-inflammatory:** Processed meat, organ meat, red meat, other fish, tomatoes, other vegetables, refined grains, high-energy beverages, low-energy beverages **Anti-inflammatory:** Beer, wine, tea, coffee, dark yellow vegetables, leafy green vegetables, fruit juice, snacks, pizza	3 inflammatory markers: IL6, CRP, TNFαR2	Incidence of colorectal cancer Incidence of colon cancer Incidence of proximal colon cancer Incidence of distal colon cancer Incidence of rectal cancer	• Risk of colorectal cancer in women and men increased by 1.32 ($HR_{highest\ vs\ lowest}$ = 1.32 (1.12-1.55); 95% CI) for subjects in the 5th quintile • Risk of colon cancer in women and men increased by 1.35 ($HR_{highest\ vs\ lowest}$ = 1.35 (1.16-1.56); 95% CI) for subjects in the 5th quintile • Risk of proximal colon cancer in women and men increased by 1.38 ($HR_{highest\ vs\ lowest}$ = 1.38 (1.13-1.68); 95% CI) for subjects in the 5th quintile • Risk of distal colon cancer in women and men increased by 1.46 ($HR_{highest\ vs\ lowest}$ = 1.46 (1.14-1.86); 95% CI) for subjects in the 5th quintile • No significant association was observed between the EDIP and rectal cancer in women and men ($HR_{highest\ vs\ lowest}$ = 1.19 (0.60-2.38); 95% CI)
Tabung et al. [92]	Prospective cohort (Nurses' Health Study and Nurses' Health Study-II), 186 314 adults, Female nurses, 30-55 years and 25-42 years Followed for 11 years	Empirical dietary inflammatory pattern	18 foods and food groups: **Pro-inflammatory:** Processed meat, organ meat, red meat, other fish, tomatoes, other vegetables, refined grains, high-energy beverages, low-energy beverages **Anti-inflammatory:** Beer, wine, tea, coffee, dark yellow vegetables, leafy green vegetables, fruit juice, snacks, pizza	3 inflammatory markers: IL6, CRP, TNFαR2	Incidence of ovarian cancer	• No significant association was observed between the EDIP and ovarian cancer risk ($HR_{highest\ vs\ lowest}$ = 0.99 (0.80-1.22); 95% CI)

Table 3. Studies on inflammatory potential of diet and health (Continued).

Author (reference)	*Study design, participants*	*Dietary inflammatory potential index*	*Nutrients and food parameters used in dietary inflammatory potential index*	*Inflammatory markers used in dietary inflammatory potential index*	*Outcomes*	*Associations/Effects observed*
Zucchetto et al. (82)	Retrospective cohort 780 adults with histologically confirmed prostate cancer Male, 46-74 years Followed for 13 years	Dietary inflammatory index	31 nutrients and food parameters: **Pro-inflammatory:** Carbohydrate, protein, total fat, SFA, cholesterol, iron **Anti-inflammatory:** PUFA, n-3 PUFA, n-6 PUFA, MUFA, fibre, vitamin A, β-carotene, vitamin D, E, B_1, B_2, B_3, B_6, folic acid, C, zinc, isoflavones, flavan-3-ol, flavones, flavonol, flavonones, anthocyanidins, alcohol, caffeine, tea	6 inflammatory markers: CRP, IL-1β, IL-4, IL-6, IL-10, TNFα	Prostate cancer mortality	• Risk of overall mortality increased by 1.42 ($HR_{highest\ vs\ lowest}$ = 1.42 (0.73–2.76); 95% CI) for subjects in the 3th tertile • No associations emerged among men with Gleason score 2–6 prostate cancer ($HR_{highest\ vs\ lowest}$ = 0.41 (0.08–2.06); 95% CI) • Risk of prostate cancer mortality among men with Gleason score 7–10 prostate cancer increased by 4.01 ($HR_{highest\ vs\ lowest}$ = 4.01 (1.25–12.86); 95% CI)
Shivappa et al. (80)	Case-control, 1225 incident colon cancer cases, 728 incident rectal cancer cases, 4154 controls hospitalised for acute non-neoplastic diseases, Female and male, 19-74 years	Dietary inflammatory index	31 nutrients and food parameters: **Pro-inflammatory:** Carbohydrate, protein, total fat, SFA, cholesterol, iron **Anti-inflammatory:** PUFA, n-3 PUFA, n-6 PUFA, MUFA, fibre, vitamin A, β-carotene, vitamin D, E, B_1, B_2, B_3, B_6, folic acid, C, zinc, isoflavones, flavan-3-ol, flavones, flavonol, flavonones, anthocyanidins, alcohol, caffeine, tea	6 inflammatory markers: CRP, IL-1β, IL-4, IL-6, IL-10, TNFα	Colorectal cancer Colon cancer Rectal cancer	• Risk of colorectal cancer increased by 1.55 ($OR_{highest\ vs\ lowest}$ = 1.55 (1.29–1.85); 95% CI) for subjects in the 5th quintile • Risk of colon cancer increased by 1.39 ($OR_{highest\ vs\ lowest}$ = 1.39 (1.13–1.71); 95% CI) for subjects in the 5th quintile • Risk of rectal cancer increased by 1.47 ($OR_{highest\ vs\ lowest}$ = 1.47 (1.14–1.90); 95% CI) for subjects in the 5th quintile
Inflammatory potential of diet and allergic diseases						

Table 3. Studies on inflammatory potential of diet and health (Continued).

Author (reference)	*Study design, participants*	*Dietary inflammatory potential index*	*Nutrients and food parameters used in dietary inflammatory potential index*	*Inflammatory markers used in dietary inflammatory potential index*	*Outcomes*	*Associations/Effects observed*
Wood et al. [21]	Case-control 99 adults with stable asthma 61 healthy controls Female and male, ≥18 years	Dietary inflammatory index	25 nutrients and food parameters: "various macronutrients, such as carbohydrates and proteins, as well as various minerals such as zinc and magnesium, and vitamins such as B_1, A, and thiamin"; "total fat, cholesterol, saturated fat, fibre, β-carotene"	3 inflammatory markers: CRP, IL-6, TNFα	Prevalence of asthma Lung function Systemic inflammation (IL-6)	• For every 1 unit increase in DII score the odds of having asthma increased by 70% (OR = 1.70 (1.03-2.14); 95% CI) • For every 1 unit increase in DII score, FEV1 decreased by 3.44 times **(**β= -3.44 (-6.50; -0.39); 95% CI) • Plasma IL-6 concentrations were positively associated with DII score (β= 0.13 (0.05-0.21); 95% CI)
Han et al. [85]	Cross-sectional (2007-2012 National Health and Nutrition Examination Survey) Female and male 8 175 children (6-17 years) 22 294 adults (18-79 years)	Dietary inflammatory index	27 nutrients and food parameters: **Pro-inflammatory:** Carbohydrate, protein, total fat, SFA, cholesterol, vitamin B_{12}, iron **Anti-inflammatory:** PUFA, n-3 PUFA, n-6 PUFA, MUFA, fibre, vitamin A, β-carotene, vitamin D, E, B_1, B_2, B_3, B6, folic acid, C, magnesium, zinc, selenium, alcohol, onion, caffeine.	6 inflammatory markers: CRP, IL-1β, IL-4, IL-6, IL-10, TNFα	Current asthma Current wheeze Lung function	• For every 1 unit increase in DII score the odds of current wheeze among adults increased by 41% (OR = 1.41 (1.17-1.70); 95% CI) • No significant association was observed between the DII and current wheeze among children (OR = 1.01 (0.92–1.10); 95% CI) • No significant association was observed between the DII and current asthma among children (OR = 1.03 (0.93–1.13); 95% CI) and adults (OR = 1.01 (0.94–1.08); 95% CI) • For every 1 unit increase in DII score, FEV1 decreased by 0.22 times **(**β= -0.22 (-0.44; -0.01); 95% CI) among adults without wheeze or asthma • For every 1 unit increase in DII score, forced vital capacity decreased by 0.35 times **(**β= -0.35 (-0.55; -0.15); 95% CI) among adults without wheeze or asthma